

WHAT IS CLAIMED IS:

1. A method for identifying a modulator of N-methyl-D-aspartate receptor (NMDA-R) signaling activity, comprising detecting the ability of an agent to modulate the phosphatase activity of a protein tyrosine phosphatase with said NMDA-R on a substrate or to modulate the binding of the protein tyrosine phosphatase to NMDA-R, thereby identifying the modulator, wherein the protein tyrosine phosphatase is capable of directly or indirectly dephosphorylating NMDA-R.

2. The method according to Claim 1, wherein said protein tyrosine phosphatase is capable of dephosphorylating a protein tyrosine kinase (PTK), which PTK phosphorylates NMDA-R.

3. The method of claim 1, wherein the protein tyrosine phosphatase is human.

4. The method of claim 1, wherein the modulator is identified by detecting its ability to modulate the phosphatase activity of the protein tyrosine phosphatase.

5. The method of claim 1, wherein the modulator is identified by detecting its ability to modulate the binding of the protein tyrosine phosphatase to the NMDA-R.

6. A method for identifying an agent as a modulator of NMDA-R signaling, comprising:

(a) contacting

(i) the agent

(ii) a protein tyrosine phosphatase and a protein tyrosine kinase (PTK) that phosphorylates NMDA-R; and

(iii) NMDA-R or a subunit thereof;

wherein either or both of (ii) and (iii) is substantially pure or recombinantly expressed;

(b) measuring the tyrosine phosphorylation level of the NMDA-R or subunit;

(c) comparing the NMDA-R tyrosine phosphorylation level in the presence of the agent with the NMDA-R tyrosine phosphorylation level in the absence of the agent,

wherein a difference in tyrosine phosphorylation levels identifies the agent as a modulator of NMDA-R signaling.

7. The method of claim 6, wherein said NMDA-R and said protein tyrosine phosphatase exist in a protein complex.

8. The method of claim 6, wherein said agent enhances the ability of the protein tyrosine phosphatase to dephosphorylate said PTK.

9. The method of claim 6, wherein said agent inhibits the ability of the protein tyrosine phosphatase to dephosphorylate said PTK.

10. The method of claim 6, wherein said agent modulates binding of the protein tyrosine phosphatase to NMDA-R.

11. The method of claim 10, wherein said agent promotes or enhances binding of the protein tyrosine phosphatase to NMDA-R.

12. The method of claim 10, wherein said agent disrupts or inhibits binding of the protein tyrosine phosphatase to NMDA-R.

13. A method for identifying a nucleic acid molecule that modulates NMDA-R signaling, comprising:

(a) obtaining a cell culture coexpressing the NMDA-R and a protein tyrosine phosphatase

(b) introducing a nucleic acid molecule encoding a gene product into a portion of the cells; thereby producing cells comprising the nucleic acid molecule;

(c) culturing the cells in (b) under conditions in which the gene product is expressed;

(d) measuring the tyrosine phosphorylation level of NMDA-R in the cells in (c) and comparing the level with that of control cells into which the nucleic acid molecule has not been introduced

wherein a difference in tyrosine phosphorylation levels identifies the nucleic acid molecule as a modulator of NMDA-R signaling.

14. A method for treating a disease mediated by abnormal NMDA-R-signaling, comprising administering a modulator of a protein tyrosine phosphatase activity, thereby

modulating the level of tyrosine phosphorylation of NMDA-R.

15. The method of claim 14, wherein the modulator modulates the ability of the protein tyrosine phosphatase to directly or indirectly dephosphorylate NMDA-R.

16. The method of claim 14, wherein the modulator modulates the ability of the protein tyrosine phosphatase to bind to NMDA-R.

17. The method of claim 14, wherein the modulator is a protein tyrosine phosphatase agonist, wherein the disease is selected from the group consisting of (i) ischemic stroke; (ii) head trauma or brain injury; (iii) Huntington's disease; (iv) spinocerebellar degeneration; (v) motor neuron diseases; (vi) epilepsy; (vii) neuropathic pain; (viii) chronic pain; (ix) alcohol tolerance and (x) depression.

18. The method of claim 14, wherein the modulator is a protein tyrosine phosphatase antagonist, wherein the disease is selected from the group consisting of (i) schizophrenia; (ii) Alzheimer disease; (iii) dementia; (iv) psychosis; (v) drug addiction; and (vi) ethanol sensitivity.

19. The method of claim 14, wherein the modulator is a protein tyrosine phosphatase antagonist and affects the ability of a protein tyrosine kinase to phosphorylate NMDA-R.